then have less angina and greater exercise tolerance even when not activating their stimulator is interesting and as yet unexplained. Perhaps this reflects the clinical course of coronary artery disease and its unpredictable nature. Braunwald and colleagues clearly recognize the difficulties in assessing treatment for angina pectoris, but they have convincingly demonstrated a significant effect of carotid sinus stimulation in their small, selected group of patients.

The clinical results presented are preliminary, and the authors stress that long-term follow-ups are not available, that the implantation of the stimulation electrodes requires an operation not without risk, that carotid sinus stimulation itself has inherent dangers (death may occur from it), and finally that careful patient selection for the procedure is essential. They also point out that carotid sinus stimulators may be useful in the management of patients with paroxysmal atrial arrhythmias unresponsive to drug therapy.

Although the report in this issue of the journal suggests that the major benefit of carotid sinus stimulation is due to a reduction in arterial pressure, a recent report[2] showed that parasympathetic stimulation to the heart by vagal nerve stimulation (which is equivalent to carotid sinus stimulation in animals) reduced coronary vascular resistance and increased coronary flow. Perhaps this is an additional mechanism by which carotid sinus stimulation improves angina pectoris. These studies must be confirmed and expanded and may lead to other new approaches to the treatment of patients with intractable angina.

From the evidence available, it appears that the technique of carotid sinus stimulation merits further study and more widespread application for the treatment of carefully selected patients with angina pectoris who are resistant to other modes of therapy. Long-term follow-up studies and studies in a group of age-matched and disease-matched control patients will be needed before this unique method of treatment can be placed in perspective.

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REFERENCES

1. Braunwald E: 13th Bowditch Lecture. The determinants of myocardial oxygen consumption. The Physiologist 12:69-93, 1969

2. Feigl EO: Parasympathetic control of coronary blood flow in dogs. Circ Res 25:509-519, 1969

3. Hamer J, Grandjean T, Melendez L, et al: Effect of propranolol (Inderal®) in angina pectoris. A preliminary report. Brit Med J 2: 720-721, 1964

4. Gilliam PMS, Prichard BNC: Use of propranolol in angina pectoris. Brit Med J 2:337-339, 1965

5. Braunwald E, Epstein SE, Glick G, et al: Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves. New Eng J Med 277:1278-1283, 1967

6. Epstein SE, Beiser GD, Goldstein RE, et al: Treatment of angina pectoris by electrical stimulation of the carotid-sinus nerves. New Eng J Med 280:971-977, 1969

7. Lown B, Levine SA: Carotid sinus: Clinical value of its stimulation. Circulation 23:766-789, 1961

8. Epstein SE, Beiser GD, Goldstein RE, et al: Circulatory effects of electrical stimulation of the carotid-sinus nerves in man. Circulation 40:269-275, 1969

Hemostatic Mechanisms In Thrombogenesis: Implications for Therapy

ELSEWHERE IN THIS JOURNAL Dr. Daniel Deykin has summarized important advances in our understanding of the physiologic mechanisms of hemostasis. He has related these mechanisms to the pathogenesis of the three types of thrombosis seen in patients: the small white thrombus that may occlude a diseased artery; the large red thrombus that may form in a vein or a chamber of the heart; and the fine fibrin thrombi that may be found in the microcirculation after diffuse clotting in the flowing blood. Of practical importance, Dr. Deykin has pointed out how the different role of the blood clotting reactions in these disorders can explain the different effectiveness of anticoagulant therapy in each. Since thrombosis may occur in any patient, physicians in all branches of medicine should profit from a careful reading of his Medical Progress article.

The hemostatic process may be divided into two overlapping steps. In the first, platelets accumulate at the site of vessel wall injury. When the endothelial lining of the vessel is broken, platelets adhere to collagen in exposed connective tissues; interact with the collagen and release ADP; and, as a result of an action of this released ADP, stick to each other to form aggregates. These early aggre-

gates are friable and easily swept away. In the second step, these unstable aggregates are converted into a platelet "cement" by a sealing process in which the individual platelets of the aggregates fuse and are reinforced by a network of fibrin spreading out into the surrounding plasma and extracellular fluid. Thrombin mediates this sealing process. Thrombin also activates an enzyme that stabilizes the supporting fibrin clot by catalyzing a chemical cross-linking of fibrin molecules. Thus, the later reactions of hemostasis depend upon the effective local activation and function of the blood clotting reactions. These reactions are triggered by contact of the blood with collagen; with a cellular lipoprotein, tissue thromboplastin, that becomes available when the vessel wall is injured; and with a phospholipid that becomes available on the altered surface of aggregated platelets.

Traditionally, three mechanisms have been invoked in the pathogenesis of thrombosis—vessel wall injury, an increased systemic coagulability of the blood, and stasis. As Deykin has emphasized, the importance of each varies in the three types of thrombosis. In the small, white arterial thrombus, blood initially continues to flow in the artery and so stasis plays a minor role. The thrombus consists of fused platelets and small amounts of fibrin. Vessel wall damage is paramount, and the thrombus grows because of the same mechanisms that operate to produce local hemostasis after vascular injury. Clotting at the platelet surface results from local activation of blood clotting and not from a systemic increase in blood coagulability. Indeed, it can occur despite a reduced coagulability of the blood induced by the coumarin anticoagulants. Now at last, after two decades of controversy, it is clear that oral anticoagulant therapy rarely prevents arterial thrombotic disease.

The large red thrombus has a very different pathogenesis. It resembles blood that has clotted in a glass tube. It may form in the absence of identifiable injury to the endothelium of a vein. Thus, a red thrombus may be produced in an experimental animal by stopping flow in a normal vein moments after the systemic injection of an activated blood clotting factor. It occurs clinically in circumstances that combine a slow, systemic activation of blood clotting with stasis—for example, postoperatively in an immobile patient with a diminished blood flow in deep leg veins in whom small amounts of activating clotting factors from the surgical site presumably gain access to the general circulation. Stasis prevents the cellular clearance in the liver of such activated blood clotting factors, permitting them to accumulate and react to form a red thrombus in the stagnant area. Because of the importance of increased systemic coagulability in the pathogenesis of the red thrombus, it is not surprising that coumarin anticoagulant therapy effectively prevents venous thrombosis and pulmonary embolism. Ironically, whereas coumarin anticoagulants have been overutilized in arterial disease, where they have little effect, they have been woefully underutilized as prophylactic therapy for patients with a high risk of venous thrombosis and pulmonary embolism.

Diffuse intravascular clotting results from the release of enough procoagulant material into the blood stream to allow fibrin to form in the circulating blood. Neither local vessel injury nor stasis is involved. The circulating fibrin is deposited as fine thrombi in the microcirculation of many organs. Whether or not these thrombi produce ischemic tissue necrosis depends upon the ability of fibrinolysis, triggered by release of plasminogen activator in the wall of the affected small vessels, to remove the fibrin. Coumarin anticoagulants act neither powerfully nor rapidly enough to stop diffuse intravascular clotting, but heparin will. However, the patient may also have a serious bleeding tendency due to consumption of clotting factors plus the anticoagulant effects of fibrin split products produced by the secondary fibrinolytic reaction. Sometimes the underlying condition causing the episode of diffuse intravascular clotting can be corrected readily, and the decision to use heparin in an individual patient requires a complete assessment of all aspects of the clinical situation.

The recent discovery of drugs that can impede platelet aggregation represents an advance of unknown therapeutic significance. Some of these drugs, such as aspirin and glycerol guiacolate, are widely used to treat minor symptoms. They deserve particular investigation in arterial thrombotic disease because of the importance of platelet aggregation in its pathogenesis. It is to be hoped that such clinical trials will avoid the mistakes of many earlier antocoagulant trials in arterial disease and will be conducted as controlled, double blind studies.

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